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Applicants respectfully traverse the rejection. The claims are directed to methods of treating diabetes or forestalling a clinical symptom indicative of diabetes. The specification defines "treating" as amelioration of a clinical symptom of diabetes on page 10, lines 10-12. Applicants respectfully submit that even if one skilled in the art were to use a transfected β cell in the claimed methods and the alleged destruction were to occur, the implanted cells would not be prevented from ameliorating a clinical symptom of diabetes or forestalling a clinical symptom indicative of diabetes prior to destruction. Thus, those skilled in the art can perform the methods as claimed to achieve the recited outcome.

Furthermore, if one skilled in the art were to use a transfected β cell in the claimed methods, those skilled in the art would have been able to increase the viability of the implanted cells according to the teaching and guidance in the specification. The specification teaches on page 48, line 23, through page 49, line 5 that immunologically incompatible cells can be used in the methods in conjunction with methods known in the art for conferring sufficient viability of the cells to achieve a particular therapeutic effect. Examples of methods taught in the specification for increasing viability of implanted cells include administration of immunosuppressive agents to render the host system tolerable to the engrafted cells (see, for example, page 49, lines 6-23); masking the cells from host immune surveillance by implanting the cells within a semipermeable barrier that allows exchange of nutrients or macromolecules but

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prevents contact with immune cells (see, for example, page 49, line 24, through page 50, line 21) or masking surface antigens on the implanted cells with binding molecules such as antibodies to prevent recognition by the immune system (see, for example, page 50, lines 21-24). Therefore, those skilled in the art would have been able to achieve the claimed outcome of treating diabetes or forestalling a clinical symptom indicative of diabetes by using transfected β islet cells in the claimed methods even if the cells were destroyed by the host immune system and, furthermore, although not required by the claims, would have been able to achieve longer term treatment of diabetes or forestalling of a clinical symptom indicative of diabetes according to the methods taught in the specification for increasing viability of implanted cells.

The Office Action alleges that the term "proinsulin" is used in a way repugnant to its usual meaning because the claims recite a proinsulin cleavage site and proinsulin is known in the art to require two cleavages to become insulin. Applicants respectfully submit that the term proinsulin as it is used in the claims and defined in the specification is consistent with the normal usage of the term in the art. The specification defines "proinsulin," on page 16, lines 9-10, as a precursor form of insulin. The specification continues on page 16, lines 15-20, teaching that the term includes modified forms of proinsulin so long as the precursor polypeptide can be processed, or modified to be processed, into a bioactive form of insulin or into an A-chain or a B-chain region of insulin which is capable of assembling into a bioactive form of insulin. The specification

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further teaches on page 26, lines 1-33 that a proinsulin used in the methods can include the two proinsulin cleavage sites found in native proinsulin, or can be a variant having additional proinsulin cleavage sites or a linker with a single proinsulin cleavage site. Applicants respectfully submit that the term "proinsulin" is understood in the art to include native proteins having a variety of different cleavage sites and variant proteins, whether man-made or naturally occurring, that are different from the bovine insulin described by Stryer, so long as these proinsulins can be processed into a bioactive form of insulin. Thus, those skilled in the art would have recognized that the proinsulins taught in the specification, including forms having a linker with a single proinsulin cleavage site, when capable of being cleaved to produce insulin, as claimed, are proinsulins according to the meaning of the term "proinsulin" as it is understood in the art.

The Office action alleges that the claims would not work with any glucose-regulated protease because not all proteases are capable of cleaving proinsulin. Applicants respectfully submit that the claims are not directed to any glucose regulated protease but, as recited in the claims, to a glucose-regulated protease capable of cleaving the proinsulin cleavage site to produce insulin. Regarding use, in the claimed methods, of a glucose-regulated protease capable of cleaving the proinsulin cleavage site to produce insulin, as acknowledged in the Office Action, the specification demonstrates that furin can be used in the claimed methods to cleave the proinsulin cleavage

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site to produce insulin and teaches a number of additional proteases for use in the invention.

Furthermore, Applicants respectfully submit that the specification teaches that a proinsulin used in the methods of the invention can contain any of a variety of proinsulin cleavage sites including those that are naturally found in proinsulin and those that are not derived from wild-type proinsulin so long as the site can be cleaved by a protease (see, for example, page 17, lines 13-32). The specification further teaches on page 37, line 23, through page 38, line 10 that the proinsulin cleavage site can be modified to the cognate recognition site for a desired protease so that the site can be cleaved by the protease. Thus, although Smeekeins et al. describes the PC2 enzyme as being highly selective for the C-peptide-A-chain junction of rat proinsulin I and only producing low levels of mature insulin from rat proinsulin I under their assay conditions, those skilled in the art would have recognized from the teaching and guidance in the specification that the PC2 enzyme can be used to produce mature insulin in the methods of the invention, for example, by incorporating the PC2 recognition site at both the C-peptide-A-chain junction and the B-chain-C-peptide junction.

Regarding claims 27 and 39, which recite a proinsulin cleavage site comprising the amino acid sequence set forth in SEQ ID NO:7, Applicants respectfully submit that the claims are directed to a glucose-regulated protease capable of cleaving the proinsulin cleavage site set forth in SEQ ID NO:7 to produce insulin. Thus, the claims are not directed to the use of a

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protease that is incapable of cleaving the proinsulin cleavage site set forth in SEQ ID NO:7. The specification provides sufficient teaching and guidance to allow those skilled in the art to use a glucose-regulated protease capable of cleaving the proinsulin cleavage site set forth in SEQ ID NO:7 to produce insulin. For example, the specification teaches on page 39, lines 4-6 that furin can cleave with high efficiency at tetrabasic amino acid sequences recited as SEQ ID NOS:7 and 8. The teaching provided in the specification is consistent with that which was known in the art because not only does Groskreutz et al. describe furin as being capable of cleaving at sites having the sequence set forth in SEQ ID NO:8, as acknowledged in the Office Action, but Smeekins et al. describes on page 8824, column 2, second full paragraph that furin efficiently cleaves sites having a sequence that is the same as that set forth in SEQ ID NO:7. Therefore, in view of the teaching and guidance provided in the specification and that which was known in the art about proteases and their recognition sites, those skilled in the art would have been able to use the claimed methods without the need for undue experimentation.

For the reasons set forth above, Applicants respectfully submit that the full scope of the claims is enabled by the specification. Accordingly, Applicants respectfully request that the rejection of claims 17-39 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 28-30 and 32-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter

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which is not adequately described in the specification. The Office Action alleges that the specification discloses just a single species of the genus of hexosamine biosynthetic pathway enzymes.

Applicants respectfully traverse the rejection. The specification defines a hexosamine synthetic pathway enzyme to be a molecule which catalyzes the conversion of glucose or a glucose metabolite such as fructose-6-phosphate, to any one of the intermediates or products within the hexosamine biosynthetic pathway (see page 21, lines 10-18). The specification further describes a number of exemplary intermediates within the hexosamine biosynthetic pathway such as glucosamine-6-phosphate, glucosamine, N-acetyl glucosamine-6-phosphate, N-acetyl glucosamine-1-phosphate and UDP-N-acetyl glucosamine (see page 19, lines 5-13). Those skilled in the art would have recognized from the description in the specification of molecule which catalyze the conversion of glucose or a glucose metabolite to intermediates such as glucosamine-6-phosphate, glucosamine, N-acetyl glucosamine-6-phosphate, N-acetyl glucosamine-1-phosphate and UDP-N-acetyl glucosamine, that Applicants had described a sufficient number of species to demonstrate possession of the claimed genus of hexosamine synthetic pathway enzymes. Accordingly, Applicants respectfully request that this ground for rejection be removed.

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CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

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